Treatment of allergic rhinitis using mobile technology with real world data

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Treatment of allergic rhinitis using mobile technology with real world data: The MASK observational pilot study

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Short title: Treatment in allergic rhinitis using an App

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Abstract

Background: Large observational implementation studies are needed to triangulate the findings from randomized control trials (RCTs) as they reflect "real world" everyday practice. In a pilot study, we attempted to provide additional and complementary insights on the real life treatment of allergic rhinitis using mobile technology.

Methods: A mobile phone app (*Allergy Diary*, freely available Google Play and Apple App stores) collects the data of daily visual analogue scales (VAS) for (i) overall allergic symptoms, (ii) nasal, ocular and asthma symptoms, (iii) work, as well as (iv) medication use using a treatment scroll list including all medications (prescribed and over the counter (OTC)) for rhinitis customized for 15 countries.

Results: A total of 2,871 users filled in 17,091 days of VAS in 2015 and 2016. Medications were reported for 9,634 days. The assessment of days appeared to be more informative than the course of the treatment as, in real life, patients do not necessarily use treatment on a daily basis; rather, they appear to increase treatment use with the loss of symptom control. The *Allergy Diary* allowed differentiation between treatments within or between classes (intranasal corticosteroid use containing medications and oral H1-antihistamines). The control of days differed between no [best control], single or multiple treatments (worst control).

Conclusions: The present study confirms the usefulness of the *Allergy Diary* in accessing and assessing everyday use and practice in allergic rhinitis. This pilot observational study uses a very simple assessment (VAS) on a mobile phone, shows novel findings and generates new hypotheses.

Key words: mHealth, mobile technology, observational study, rhinitis, treatment

Abbreviations

AHA: Active and Healthy Aging

AR: allergic rhinitis

ARIA: Allergic Rhinitis and its Impact on Asthma

AZE: Azelastine

EIP: European Innovation Partnership

EU: European Union

FF: Fluticasone furoate

FP: Fluticasone propionate

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

ICT: information and communications technology

INCS: Intranasal corticosteroid

MACVIA: Contre les MAladies Chroniques pour un VIellissement Actif

MASK: MACVIA-ARIA Sentinel NetworK

MF: Mometasone furoate

MP-AzeFlu: Azelastine-Fluticasone propionate

OAH: Oral H_1-antihistamines

OTC: over the counter

RCT: randomized controlled trial

RTSS: rhinoconjunctivitis total symptom score

REST: Restricted analysis

TNSS: Total nasal symptom score

VAS: visual analogue scale

Introduction

The treatment of allergic rhinitis (AR) is complex as many drugs are available in oral and/or topical formulations. Many guidelines for AR are evidence-based and have led to a better understanding and management of AR. However, guidelines are mostly based on randomized controlled trials (RCTs), typically undertaken on highly selected populations, often with limited/unclear generalizability to routine care contexts (1-3).

Large observational implementation studies are needed to triangulate RCT as they reflect "real world" every day use and practice more closely than RCTs in terms of the heterogeneous patient populations included, and the variety of medical interventions assessed (4). In RCTs, each subject is randomly assigned to a treatment or control group, whereas observational studies examine the possible effect of a treatment on subjects where the investigator has no control over the experiment and cannot randomize subject allocation (5). However, observational studies provide clinically relevant information in addition to RCTs.

MASK-rhinitis (MACVIA-ARIA Sentinel NetworK for allergic rhinitis), an information and communications technology (ICT) system centered around the patient (6-8), is one of the implementation tools of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) (9, 10). A mobile phone app (*Allergy Diary)*, launched in 22 countries (11), uses visual analogue scales (VAS) to assess rhinitis control and work impairment (12), as well as a treatment scroll list including all medications customized for each country. The use of mobile health applications to conduct observational clinical studies requires the establishment of feasibility.

This pilot study was undertaken to provide additional and complementary insights to evidence derived from RCTs in the real life treatment of AR. The *Allergy Diary*(11) was used to assess the control of rhinitis by medications.

Methods

Design of the study

This prospective observational study of a mobile application – the *Allergy Diary* – was used to assess self-reported medication use.

The objectives of this study were (i) to report the median VAS global-measured values depending on the treatment received, (ii) to undertake a sensitivity analysis by comparing the results for one day of treatment, the full data set and a restricted data set (i.e. 2016 and the first two weeks of treatment), (iii) to investigate users receiving single prescribed treatments (MP-AzeFlu, FF or MP monotherapy for rhinitis) and those receiving several treatments for rhinitis on the same day (co-medication for rhinitis) and (iv) to assess initial severity assessed on the first day of use of the App on the treatment reported by users.

Users

All consecutive users from May 21, 2015 to November 8, 2016 were included with no exclusion criteria. Some demographic characteristics (age, sex, country and language) were recorded. The *Allergy Diary* was used by people who found it on the internet, Apple App store, Google Play or any other way. The pages of the App are on the Euforea-ARIA website (www.euforea.eu/about-us/aria.html).. A few users were clinic patients who were asked by their physicians to use the app. Users were not requested to complete the diary for a minimum of days. However, due to anonymization of data, no specific information on the route of access to the app could be gathered as previously reported (11, 13).

Setting

Users from 15 countries filled in the *Allergy Diary* (Table 1).

Allergy Diary

Geolocalized users assess their daily symptom control using the touchscreen functionality on their smart phone to click on five consecutive VAS (i.e. general, nasal and ocular symptoms, asthma and work) (Figure 1 online). Users input their daily medications using a scroll list which contains all country-specific OTC and prescribed medications available (Figure 2 online). The list has been populated using IMS data.

Ethics

The Allergy Diary is CE1 registered but it was not considered by the Ethical Committee of the Cologne Hospital of the MHRA (Medicines and Healthcare products Regulatory Agency - GOV.UK) as a medical device given that it does not provide any recommendations concerning treatment or diagnosis. The terms of use were translated into all languages and customized according to the legislation of each country, allowing the use of the results for research purposes. The example of the UK terms of use have been provided in a previous paper (11)**.**

The data were anonymized except for the geolocalized data which are never totally anonymous. This issue was carefully considered in the first paper on the *Allergy Diary.* (11)

An Independent Review Board approval was not required.

Outcomes

In this study, initial characteristics (Table 1 online) (11), four VAS measurements (VAS-global measured, VAS-nasal, VAS-ocular, and VAS-work, Table 2 online) and a calculated VAS-global calculated score (VAS-nasal + VAS-ocular divided by 2) were considered. The VAS-asthma was not analyzed as there was a change in the question on June 1, 2016. VAS levels range from zero (not at all bothersome) to 100 (very bothersome). Independency of VAS questions was previously assessed using the Bland and Altman regression analysis (13, 14).

Days reported by users included days with or without treatment.

The present study is another *Allergy Diary* study. None of the data used in the first paper (11) were used in this study. Data of the second paper were used but the analysis was totally different since we analyzed medication effects whereas in the former paper the focus was on work productivity (13).

Selection of medications

The International Nonproprietary Names classification was used for drug nomenclature (15). Monotherapy was defined as days when only one single medication for rhinitis was taken. Poly-medication (co-medication) was defined as days with two or more medications for rhinitis. Asthma medications were not considered in poly-medication.

Avamys® (FF) and Dymista® (MP-AzeFlu) were the only prescribed medications. MF is OTC in the UK (since mid 2015), Sweden (since Feb 2013), Finland (since Nov 2012) and we excluded users with possible OTC drugs.

Biases

There are potential measurement biases when using apps since the information collected is usually restricted. The self-reported nature of the data represents another bias inherent to App usage. A bias might be introduced because app users may be a selected subset, and are therefore not fully representative of all patients with rhinitis. Finally, it is not known whether users fill in their information before of after treatment for a given day.

Size of the study

In this exploratory pilot study, all registered users between May 21, 2015 and November 8, 2016 were included to obtain the best possible estimates for the specified time window.

Statistical methods

A non-Gaussian distribution was found for the data. Non-parametric tests and medians (and percentiles) were used.

Some users reported VAS scores more than once a day. Before analysis, we proposed that if the same treatment was reported and the daily variation was under 30%, the highest VAS score would be used as previously (13). In the full data set, there were 631 days with multiple values, and of these only 133 (1.4%) had a variation > 30%. We decided that this number was not sufficient enough to impact the results and we used the highest value for the day.

Analysis of the data

The study was not a longitudinal study because (i) there was an insufficient number of users reporting data over a period of 5 days (335), (ii) there was no clear pattern of treatment in users, (iii) most users did not report a stable and continuous period of treatment and (iv) many users modified their treatment during the reporting period. Moreover, in the study, users are unselected and it is not known whether the first day of use was the first day of treatment. Although there may be causal inferences, we used cross-sectional data for days of treatment. We analyzed the full data set and performed the following sensitivity analyses: (i) a restricted analysis (REST) was performed on up to the first 15 days of treatment in users who initiated their study in 2016, and (ii) the first day of reporting was analyzed since there was a higher level of VAS on day 1 than on the other days and there were more users with a single day than with multiple days.

Medications used and compliance to treatment: All users were investigated for 2015 and 2016 and the number of days of reporting VAS levels were assessed. We then studied 2016 and examined the compliance to treatment in users who reported 5-7 days, 8-15 days and >16 days. In the latter group, only the first 30 days were investigated. Compliant users were those reporting ≥ 80% consecutive days and ≥80% days with the same treatment. Uncompliant users were those reporting <80% days with the same treatment. Discontinuous users were those reporting < 80% consecutive days and ≥80% days with same treatment. We then checked the number of medications reported during the period of examination.

Control of the disease: Using the full data set and REST, we studied median VAS levels for medications reported for at least 1,000 days and for days without medications. We used the global measured VAS as a primary end point and the other VAS measures (nose, eyes, work) as secondary end points (12). As this was a pilot study, only the primary end point was analyzed using the Kruskal-Wallis test with Dunn's post hoc analysis.

Prescribed medications: We then focussed on the three medications always prescribed i.e. those not available over the counter (MP-AzeFlu, FF and MF). For MF, we carefully checked the dates of OTC introduction for the different molecules in the different countries. We first analysed the frequency of days with monotherapy (FF and MF) or MP-AzeFlu and days with added medications (co-medication). We then compared VAS global-measured levels the first day of use, REST and full data. Data were analyzed using the Kruskal-Wallis test with Dunn's post hoc analysis.

Results

Users

A total of 2,871 users filled in 17,091 days of VAS (Figure 1). There were 39% females, 44% males and 17% of unknow. The mean age was 37 ± 17 years. The age of the users (by days) is reported in Figure 3 online and shows that the App was used from 12 to 80 years of age with a peak at 30-49 years.

Medications were reported for 9,634 days and no medications for 7,457 days. 2,741 users (1,686 with medication) responded "Yes" to Q1 (i.e. "Do you have rhinitis?) and 130 users (52 with medication) responded "No" but ticked any nasal symptom (Q3). VAS-work was only included in the App after June 1, 2016 and fewer days with VAS are available (Table 1).

Among the 17,091 VAS days, all users filled in VAS-nasal and VAS-ocular but 436 days were not filled in for VAS-global measured ("No" to Q1).

Treatments and compliance

The number of reported days per user ranged from one (1,539 users) to over 60 (2-7 days: 911 users, 8-15 days: 149 users, >15 days: 266 users). Among the 2016 users, 98 reported 5 to 7 days, 85 8-14 days and 181 over 15 days (Table 2). Only 33.9% of users reported a single mediation and 42.1% reporting over eight days of VAS used three treatments. In users reporting five or more days of VAS, compliance to treatment ranged from 32.9% to 40.8% (Table 2).

The treatments reported included 504 drugs and 86 INNs or combinations associated to medications. 475 users received an asthma treatment.

Overall results

Data obtained were extremely consistent for different VAS measurements (global measured, nose, eyes and work) or different analyses (full data set and restricted data set across all outcomes) (Table 3). In the full data set, VAS scores were greater on days with treatment (median, 25-75 percentiles for VAS global measured: 25 (9-50)) than on days without treatment (11 (2-33)) ($p<0.0001$). Similar levels of VAS were reported on days without treatment in users who never reported any medication

(15 (0-47)) and in those who were sometimes treated (Uncompliant: 15 (5-37)). There were minimal differences in recorded VAS scores between MP-AzeFlu (19 (8-45)), FF (22 (4-52)) and MF (25 (11-48)).

The median scores for the six medications imputed for over 1,000 days showed that days with any of the three medications containing INCS had a lower VAS global measured level than days in which OAH were reported.

Single therapy and co-medication

The results were extremely consistent since, for all medications apart from desloratadine, days under monotherapy (or MP-AzeFlu) had significantly lower VAS-global measured median levels than days with co-medication (Table 4).

Prescribed medications

Only three medications containing INCS were exclusively prescribed. MF was OTC in some countries but the users were low in number and therefore not included in the analysis. There were major differences between treatments in the percentage of mono- and co-medication including OAH used. MP-AzeFlu was used more often alone (64-68%) than FF (32-37%) or MF (38-46%) and these trends were found in day 1 and persisted across the study (Figure 2).

The results for the three INCS-containing medications as rhinitis-monotherapy, treatment with an oral H1-antihistamine (OAH) or any other medication for rhinitis (poly-medication) are presented in Table 5. For the full data set, MP-AzeFlu had a median VAS score (14(6-33,5)) similar to FF monotherapy (15(0-39)) and MF monotherapy (17(8-32)), but significantly lower than FF + OAH (31(14-58)) or MF + OAH 34(16-58). On the other hand, MP-AzeFlu + OAH had a VAS score (33(13,5-54)) similar to FF or MF + OAH. Similar trends were observed for REST and the results of Day 1. VAS levels were higher for Day 1 than for REST and the full data set for all medications and combinations.

Discussion

The feasibility of using mobile health applications to conduct observational clinical studies requires assessment: (i) The present study confirms the usefulness of the *Allergy Diary* in accessing and assessing everyday use and practice in AR. (ii) This observational study, using a very simple assessment (VAS) on a cell phone, shows novel concepts concerning our knowledge of AR treatment and should be considered as an exploratory pilot study hypothesis generating. (iii) In real life, the assessment of days appears to be informative. (iv) The *Allergy Diary* allows the differentiation between treatments. (v) The control of days differs between no (best control), single or multiple treatments (worst control).

Strengths and limitations

Smart devices and Internet-based applications are already used in rhinitis (16-21) but none have assessed real life treatment in a large number of users. The strengths of mobile technology include its wide acceptance and easy use, but there is a need to use appropriate questions, and results should be assessed by pilot studies. This pilot study was based on 2,871 users who filled, in 17,091 days of VAS.

Data obtained were extremely consistent for different VAS measurements (global measured, nose, eyes and work) or different analyses (full data set, day 1 and REST). In a previous paper, we showed that there were strong to very strong correlations between the overall control of rhinitis and work VAS (13).

In the present study, the definition of having rhinitis is purely users' dependent. Since the definition of rhinitis is not clear to the users, other conditions such chronic rhinosinusitis, or nasal septal deviation could have been considered as allergic rhinitis. Although the App does not allow to assess all the analyses proposed to differentiate between these diseases, sneezers and blockers will be differentiated in the next analysis as previously done (22). However, we did not do it in the present study (i) because an insufficient number of users and (ii) in this pilot analysis, we wanted to mimic a real life study. From our experience in GPs, differentiation between allergic and non-allergic rhinitis is difficult and most GPs do not attempt to make any differences between nasal symptoms (1, 23, 24).

The study as already mentioned has no pretentions of reflecting the general population because (i) only a shot was taken into account, (ii) people using an App are not representative of the general population and (iii) the users reported few days few days. However, the sample size is important and according to the Law of Large Numbers, the characteristics of a random sample approach the statistical characteristics of the population from which the sample is extracted when the sample size increases.

Compliance is difficult to analyse without a real assessment by electronic pill counters or inhalers. These do not exist for nasal products or are just in testing. Questionnaires can be used but it appears that real life data are more appropriate. However, it should be emphasized that users may not report all medications used.

Longitudinal data capture was very challenging because treatment trajectories are specific for almost each user and most users have gaps in treatment days when they are well-controlled, hence the focus on a cross-sectional analysis on days of treatment.

Interpretation of the results and generalizability

The real world assessment of the *Allergy Diary* using VAS allows assessment of treatment efficacy by days, which may represent a more objective estimation of AR treatments than patients' comments since: (i) it is known that AR is a highly variable disease, and control varies widely between days in relation to allergen exposure, (ii) patients are not always compliant with their treatment, (iii) patients often stop treatment when they feel better (as found by the study but not shown) and (iv) patients increase their treatment when uncontrolled.

VAS scores were greater on treatment days than on days without treatment, suggesting that users reporting no treatment had milder disease than those who were occasionally treated. However, median VAS levels on days without treatment were similar in users who never reported any medication use and in those who were occasionally treated. Days without treatment were better controlled than days with treatment and days with a single treatment were better controlled than days with multiple treatments. These data suggest that, in real life, patients treat themselves when they suffer from symptoms and stop their treatment when they are controlled. This accords with previous data (25, 26). This study, using objective data, confirmed that adherence is poor. Most patients with rhinitis may have mild and/or intermittent disease that does not need a regular treatment to achieve control. The concept of pro-active medication (27) - the patient starting treatment when experiencing symptoms and continuing for a few days after getting control - may be of great interest and could be tested with the App. In asthma, self-guided treatment was found to be of interest (27-29). Such real life findings may ultimately affect the way in which guidelines are constructed to align them more with human behaviour.

This observational study made it possible to differentiate OAH and INCS, confirming known data, (30) but may be able to differentiate between OAH when more data are analyzed. It could also differentiate the three medications containing INCS: FF, MF and MP-AZeFlu and confirm previous studies, (31) extending our understanding of how AR treatment is used. RCTs showed that MP-AzeFlu is more effective than single components available in pharmacies (32) or components using the same formulation (33). However, observational studies comparing prescribed medications containing INCS are not available. In the present study, a clear difference was found between medications. Disease control assessed by VAS was similar in users who reported a single treatment for the three medications and was similarly increased in those with co-medication. However, a major difference is that around one third of MP-AzeFlu received the treatment without co-medication whereas FF or MF users required co-medication in 31 to 46%. Although this is a pilot study, over 1,000 days of treatment were reported for each medication. A bias may however be confounding by indication.

Conclusions

This observational study shows highly consistent results between different outcomes (VAS levels), days of treatment or medications. It appears possible to use this approach to better tailor treatments to individuals.

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Table 1. Country and number of users recording Visual Analogue Scale score using the *Allergy Diary* in the full data set

Country	VAS measurements (days)				
Austria	81 (55.5%)	48	4	13	146
Belgium	22 (51.2%)	18	1	2	43
Denmark	12 (52.2%)	8	1	2	23
Finland	10 (43.5%)	8	2	3	23
France	232 (69.0%)	84	7	13	336
Germany	74 (50.7%)	52	6	14	146
Greece	8 (57.1%)	5	0	1	14
Italy	379 (55.4%)	211	38	56	684
Lithuania	18 (35.3%)	16	5	12	51
Netherland	60 (54.5%)	35	7	8	110
Poland	157 (60.1%)	82	10	12	261
Portugal	305 (49.9%)	226	28	52	611
Spain	64 (28.3%)	59	31	72	226
Sweden	18 (52.9%)	12	2	2	34
UK	86 (60.1%)	43	6	8	143
Total	1526 (53.5%)	907 (31.8%)	148 (5.2%)	270 (9.5%)	2851

Data from Australia, Brazil, Canada, Mexico and Switzerland were excluded due to the low number of users (enrolment started in October 2016)

Table 2: Compliance to treatment in users reporting ≥ 5 days of VAS in 2016

Treatment reporting (days)	N	Pattern**			Number of treatments during the reporting			
		Compliant	Discontinuous	Un-compliant	1	2	3	≥4
5-7	98	40 (40.8%)	12 (10.2%)	46 (47%)	41 (41.8%)	33 (33.7%)	21 (21.4%)	3 (3.1%)
8-14	85	28 (32.9%)	17 (20%)	40 (47.1%)	27 (31.7%)	20 (23.5%)	19 (22.3%)	19 (22.3%)
15-30 *	181	71 (39.2%)	18 (10%)	92 (50.1%)	52 (28.7%)	55 (30.4%)	37 (19.9%)	37 (19.9%)

*: Assessment of day 1- up to day 30 in users who reported ≥ 15 days of VAS

**: Compliant: reporting ≥ 80% consecutive days and ≥80% days with treatment. Un-compliant: reporting <80% days with treatment, Discontinuous: reporting < 80% consecutive days and ≥80% days with treatment.

Table 3: Median Visual Analogue scale [VAS] scores recorded in *Allergy* Diary according to inputted rhinitis treatment

	VAS Count	Users	Eyes VAS	Nose VAS	Asthma VAS	global_ meas VAS	global_ calc VAS	fit_work VAS
No treatment	7457	1712	5 [0-24] [7457]	13 [1-39] [7457]	0 [0-14] [5167]	13 [1-38] [7250]	11 [2-33] [7457]	5 [0-19] [2365]
No treatment rest	4038	1602	9 [0-32,75] [4038]	22 [5-50] [4038]	1 [0-18] [2462]	22 [5-50] [3878]	19 [5-41] [4038]	9 [0-28] [1170]
No medication [at any time for the user]	3168	1116	6 [0-27] [3168]	16 [1-47] [3168]	0 [0-13] [2132]	15 [0-47] a [3021]	13,5 [1,5-37] [3168]	5[0-19] [1028]
No medication [for some days only for the user]	10109	596	6 [0-26] [10109]	16 [5-38] [10109]	1 [0-18] [7139]	15 [5-37] b [9929]	12,5 [4-32] [10109]	8[0-24] [3129]
With treatment	9634	1755	10 [0-35] [9634]	25 [9-51] [9634]	6 [0-29] [7001]	25 [9-50] c [9408]	19 [7-42] [9634]	14 [3,25-37] [2834]
With treatment rest	5489	1600	14 [1-41] [5489]	30 [11-56] [5489]	8 [0-36] [3793]	31 [13-55] [5332]	25 [10-47] [5489]	18 [5-42] [1514]
FF	1252	226	10 [0-33] [1252]	22 [4-51] [1252]	4 [0-32] [954]	22 [4-52] d [1223]	18 [3-42] [1252]	16 [4-38] [386]
FF rest	783	200	13 [0-37] [783]	28 [11-53,5] [783]	9 [0-36] [557]	28 [11-53,5] [771]	22,5[8,5-45] [783]	17[5,25-37] [254]
MP-AzeFlu	1628	195	9 [0-28] [1628]	20 [7-46] [1628]	4 [0-22] [1244]	19 [8-45] e [1601]	15 [6-38] [1628]	10 [2-27] [524]
MP-AzeFlu rest	748	158	13 [2-33,25] [748]	27 [11-53] [748]	4,5 [0-24] [526]	27 [12-50] [732]	23 [9-42,625] [748]	21,5 [8-37,25] [236]
Desloratadine	1102	319	19 [1-48] [1102]	35 [13-58] [1102]	12 [0-41] [767]	34 [15-55] f [1076]	28 [12-51] [1102]	28 [10-50] [325]
Desloratadine rest	732	283	20 [1-47,25] [732]	35 [13-61] [732]	8 [0-34] [482]	36 [16-59] [722]	28 [11-51,5] [732]	23 [9-47] [205]
Cetirizine	1293	378	13 [1-47] [1293]	23 [8-57] [1293]	8 [0-31] [866]	28 [9-58] g [1270]	22 [7-49,5] [1293]	13 [6-40] [375]
Cetirizine rest	945	356	14 [1-48] [945]	28 [10-59] [945]	7 [0-34] [604]	32 [12-60] [924]	25,5 [9-50,5] [945]	21 [7-46] [229]

MF	1368	211	9 [0-32] [1368]	24 [11-48] [1368]	3 [0-17] [951]	25 [11-48] h [1366]	18 [9-38] [1368]	13 [4,75-36] [440]
MF rest	693	193	12 [0-38] [693]	28 [12-56] [693]	3 [0-29,5] [447]	29 [12,5-55] [691]	22,5 [9,5-45] [693]	9 [0-29] [185]

Rest: restricted to 15 days survey in 2016 study, meas: measured, calc: calculated

Results in medians and [25-75 percentiles]

MP-AzeFlu: Intranasal azelastine and fluticasone propionate, FF: fluticasone furoate; MF: mometasone furoate;

Square brackets: number of days

Statistical analysis

a, b, c: Kruskall Wallis p<0.0001, Bonferroni-Dunn's post hoc analysis: a/b: NS, a/c: p<0.05, b/c: p<0.05

d,e,f,g,h: Kruskall Wallis p<0.0001, Bonferroni-Dunn's post hoc analysis

	AzeFlu	**FF**	**Desloratadine**	**Cetirizine**	**MF**
AzeFlu (e)		NS	P<0.05	P<0.05	P<0.05
FF (d)	NS		P<0.05	P<0.05	P<0.05
Desloratadine (f)	P<0.05	P<0.05		P<0.05	P<0.05
Cetirizine (g)	P<0.05	P<0.05	P<0.05		
MF (h)	P<0.05	P<0.05	P<0.05	NS	

Table 4: Daily global measured VAS (full data set)

	MP AzeFlu		FF		MF		Loratadine		Cetirizine	
	Single	**CoM**	**Single**	**CoM**	**Single**	**CoM**	**Single**	**CoM**	**Single**	**CoM**
N	1039	589	406	846	625	743	610	492	622	671
Minimum	0	0	0	0	0	0	0	0	0	0
Maximum	100	99	100	100	100	100	100	100	100	100
Median	14.0	32.0	15.0	25.5	17.0	34.0	34.0	35.0	22.0	33.0
25%	6.0	13.0	0.0	6.0	8.0	17.0	14.0	15.0	8.0	10.0
75%	33.5	54.0	39.0	55.0	32.0	55.0	53.0	59.0	53.0	61.5
	p<0.001		**p<0.001**		**p<0.001**		**NS**		**p<0.001**	

Single: single treatment, Poly:, p value by Mann-Whitney U test

Table 5: Median global visual analogue scale scores measured in days with INCS-containing medications

		Full data set		Restricted data set [REST]		Day 1
		Median [25-75] [day counts]	Users	Median [25-75] [day counts]	Users	Median [25-75] [day counts]
FF		15[0-39] [377]	107	21[4-44,25] [222]	92	40[24-54] [57]
	+ OAH	25[5-55] [803]	149	31[14-58] [514]	134	59[33-76] [93]
	+ other co-medication	26[12-34] [43]	19	25[10,5-34] [35]	14	23[13,5-23] [3]
AMP-		14[6-33,5] [1023]	149	21,5[9-44] [458]	123	36[16,25-58,25] [90]

Aze Flu	+ OAH	33[13,5-54] [459]	71	41[20,75-59,25] [228]	56	56[27,5-70] [32]
	+ other co-medication	25[13-54] [119]	31	24[10,75-42] [46]	14	44[30,25-83,25] [12]
MF		17[8-32] [623]	99	19[6-38] [270]	89	32[18-57] [53]
	+ OAH	34[16-58] [606]	137	40[17-62] [386]	124	54,5[30-78] [76]
	+ other co-medication	31[21-48] [137]	20	30[19,5-50] [35]	14	53[50-58] [9]

FF: fluticasone furoate; OAH: oral anti-histamine; MF: mometasone furoate, MP-AzeFlu: Intranasal azelastine and fluticasone propionate,

Statistical analysis

	AzeFlu	AzeFlu + OHA	FF	FF + OHA	MF	MF + OHA
AzeFlu		**P<0.05**	NS	**P<0.05**	NS	**P<0.05**
AzeFlu + OHA	**P<0.05**		**P<0.05**	**P<0.05**	**P<0.05**	NS
FF	NS	**P<0.05**		**P<0.05**	NS	**P<0.05**
FF + OHA	**P<0.05**	NS	**P<0.05**		**P<0.05**	**P<0.05**
MF	NS	**P<0.05**	NS	**P<0.05**		**P<0.05**
MF + OHA	**P<0.05**	NS	**P<0.05**	**P<0.05**	**P<0.05**	

Statistical analysis by Kruskall-Wallis test ($p<0.0001$) and Dunn' post hoc analysis

P<0.05: significant for full data set and REST, $p<0.05$: **significant** for full data set only

Users with co-medication other than OAH were not included due to their low number

Figure 1: Flow chart

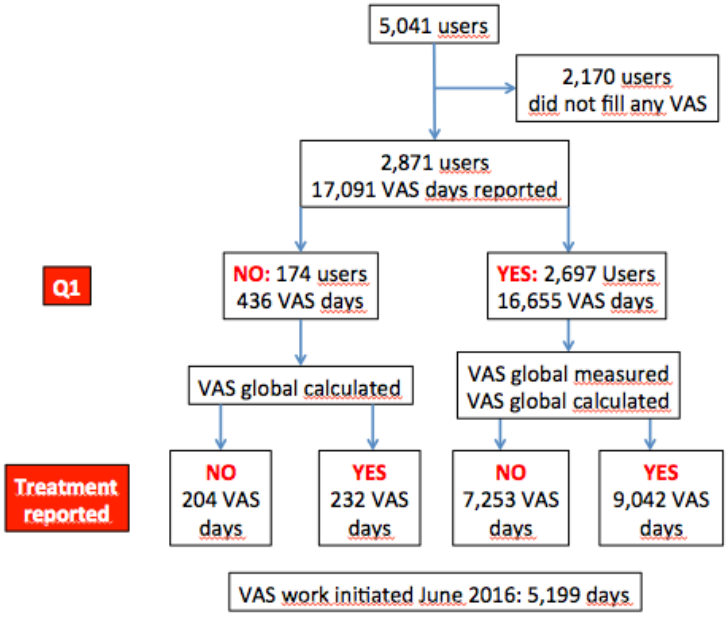

Figure 2: Percentage of days with single treatment